REMARKS

A final Office Action was mailed in the above-captioned application on April 24, 2008. Claims 1, 3, and 5-20 were pending in the application. Claims 1, 3, and 5-20 were rejected. An Amendment and Response document was submitted in response to the Office Action on June 23, 2008. An Advisory Action was mailed on July 16, 2008. The Advisory Action indicated that the claim amendments would be entered, but did not place the application in condition for allowance. Request for Continued Examination under 37 C.F.R. § 1.114 was submitted on August 22, 2008 and has been entered. Claim 1 was amended and claims 11-17 were cancelled.

This Amendment and Response document is being submitted in response to the Office Action dated November 3, 2008 where Claims 1, 3, 5-10, 19 and 20 are pending. Applicant has amended Claims 3 and 19. These amendments have been made to place to claims in better form for examination and to further obviate the 35 U.S.C 102(b), 103(a) and 112 rejections. It is believed that none of these amendments constitute new matter.

Rejections Under 35 U.S.C. § 112 indefiniteness

The Examiner has rejected claims 2 and 19 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants believe that the Examiner has made an inadvertent error in rejecting Claim 2 as Claim 2 was previously cancelled. Applicants do however note that Claim 3 recites the limitation "the nucleic acid exposing step" as rejected by the Examiner for Claim 2. Applicants have amended Claim 3 to remove the insufficient antecedent basis and Claim 19 has been amended to remove the unclear term. Withdrawal of this is rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102(b) Hu

The Examiner has rejected Claims 1, 3, 9-10 and 19 under 35 U.S.C. § 102(b) as being anticipated by Hu (U.S. Patent No. 5,939,251). Applicants have amended Claim 3 and 19. In addition, Applicants respectfully traverse this rejection.

A *prima facie* case of anticipation requires that a single publication teach, either expressly or inherently, each and every element or limitation of the claim, including any functional limitations. M.P.E.P. § 2131. According to the Examiner, Hu teaches a method of performing *in situ* PCR within a solid support having multiple compartments, wherein the cells are directly fixed on the solid support. The Examiner has also specifically pointed out that Hu teaches a method comprising: determining whether amplified nucleic acids in a PCR solution contains the target nucleic acid (col. 6, lines 25-35).

Applicants submit that the Examiner has misinterpreted the term *in situ* in the context of *in situ* PCT. In the Office Action on page 4 the Examiner states "the teaching of *in situ* PCR necessarily means the cell sample was treated in some manner to allow amplification". The Applicants contend that *in situ* PCR, is commonly known by those skilled in the art to be a PCR reaction that actually takes place inside the cell on a slide and is performed on fixed tissue or cells. The *in situ* PCR method is an improvement of an *in situ* hybridization (ISH) that was developed to detect a nucleic acid amplified in a cell while maintaining the conformation of the cell (see, e.g., column 2, lines 5-8, and column 6, lines 25-27 of Hu). Determining the existence of the target nucleic acid in a PCR solution is claimed in Claim 1 of the present invention and thus the amplified gene to be detected exists extracellularly, which Hu does not teach nor suggest. Hu teaches a method for performing a molecular biological reaction such as an *in situ* polymerase chain reaction (PCR) and *in situ* hybridization (ISH) (column 1, line 14; column 6, line 22 of Hu). The *in situ* PCR method of Hu is fundamentally different than the claimed invention in that Hu teaches a method used for detecting intracellular localization of a target nucleic acid (i.e., detecting a target nucleic acid existing in a cell or tissue). Therefore, the Applicants contend that Hu does not anticipate the invention as claimed.

Additionally, Applicants would like to point out that in the case of *in situ* PCR, an amplified gene to be detected could not exist extracellularly because of a washing step after amplification of a gene *in situ* (see for example, Villeponteau et al. U.S. Patent No.5,776,679, column 42, lines 41-42). Furthermore, because the washing step after amplification *in situ* is important *in situ* PCR, one skilled in the art would know that the washing step cannot easily be

replaced with another step. Needless to say, one skilled in the art cannot delete such an important step of washing a cell after amplification of a gene *in situ* and this the amplified gene to be detected could not exist extracellularly as taught in the present invention.

Thus, for the reasons discussed above, Hu does not disclose or suggest each and every element of Claims 1, 3, 9-10 and 19. Accordingly, Hu does not anticipate Claims 1, 3, 9-10 and 19, and Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a) Hu in view of Villeponteau et al.

The Examiner has rejected Claim 5 under 35 U.S.C. § 103(a) as being unpatentable over Hu (U.S. Patent No. 5,939,251) in view of Villeponteau et al. (U.S. Patent No. 5,776,679). The Examiner has stated that Hu does not expressly teach the labeling of nucleic acids during PCR or detection of PCR products through electrophoresis. However, the Examiner states that Villeponteau et al., teaches labeling nucleic acids during *in situ* PCR through the incorporation of labeled nucleotides (column 42, line 50-65). Thus it would be *prima facie* obvious to a skilled artisan to incorporate labeled nucleotides into the *in situ* PCR of Hu.

Applicants respectfully traverse this rejection. The disclosure of Villeponteau et al. does not overcome the deficiencies of Hu as discussed above and thus neither Hu nor Villeponteau et al., whether considered alone or in combination teach each and every element of Claim 5.

A *prima facie* case of obviousness has three distinct requirements. First, the references must teach or suggest every claim element. M.P.E.P. §§ 2142 and 2143.03. Second, there must be a motivation to modify or combine the teachings of the cited references. M.P.E.P. §§ 2143 and 2143.01. Third, there must be a reasonable expectation of success in performing the modified or combined teachings of the references. M.P.E.P. § 2143.02.

The Applicants contend that neither Hu nor Villeponteau et al. teach or suggest the step of "determining whether amplified nucleic acids in a PCR solution contain the target nucleic acid. As mentioned above, Hu teaches an *in situ* PCR method which is not the same as the detection method of the invention as claimed (due to amplification of the target within the cell or tissue and the important washing step, for example).

Additionally, no reasoning or evidence is provided explaining why one skilled in the art would have been motivated to modify the teaching of Hu regarding the *in situ* PCR method in order to arrive at the nucleic acid detection method of the present invention. "Rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1396, quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). No reasoning has been provided in the rejection. According to the *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in* KSR International Co. v. Teleflex Inc., 72 Fed. Reg. 57526 (October 10, 2007), the Examiner must provide some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. In the present case, no explanation or support has been provided to show that one skilled in the art would have been motivated to modify the teaching of Hu regarding the *in situ* PCR method in order to arrive at the nucleic acid detection method of the present invention. In addition, on pages 30-31 of the Specification, a discussion is provided as to the drawbacks of *in situ* PCR including tedious condition settings, falling behind in terms of reproducibility, and setting off many non-specific reactions which makes it difficult to distinguish the non-specific products of the amplification from the target specific product in the cells. Thus Applicant contends that the nucleic acid detection method of the present invention is thus different from the *in situ* PCR method.

Therefore, even combining the teachings of Hu and Villeponteau et al., one does not arrive at the invention recited in Claim 5. Because none of these references, alone or combined, teach each and every element of Claim 5, Applicants submit that Claim 5 is patentable over the cited references. The Applicants thus respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Applicants notes that the Examiner has also stated in regards to Claim 20, that the detection of PCR products through electrophoresis was well known as a standard method of PCR

product detection and that Villeponteau et al teaches such an electrophoresis method (column 31, example 3). Based on the reasons provided above, the Applicants assert that neither Hu nor Villeponteau et al., whether considered alone or in combination teach each and every element of Claim 20 and thus a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103(a) Hu in view of Villeponteau et al. in further view of Stapleton et al.

The Examiner has rejected Claims 6-8 under 35 U.S.C. § 103(a) as being unpatentable over Hu (U.S. Patent No. 5,939,251) in view of Villeponteau et al. (U.S. Patent No. 5,776,679) as applied to Claim 5 and in further view of Stapleton et al. (U.S. Patent No. 6,103,192). The Examiner has stated that the previously applied references do not expressly teach the detection of labeled PCR products through hybridization to an immobilized probe in microarray format. The Examiner states that Stapleton et al teaches a method wherein various biological specimens are collected, dried, transported, stored and processed on matrixes which adhere cells and viruses. Additionally as concluded by the Examiner, Stapleton states that "such a detection system eliminates the need for gel electrophoresis,. . ., and allows for multiple oligonucleotide sequences at different array positions to be analyzed in the same detection reaction". Even if the combination of Hu and Villeponteau et al. and Stapleton et al. is made as suggested by the Examiner, none of the references alone, nor the combination of references discloses the claimed invention, namely the claimed nucleic acid detection method that includes the step of "determining whether amplified nucleic acids in a PCR solution contain the target nucleic acid. More specifically, the *in situ* PCR method of Hu is a method used for detecting intracellular localization of a target nucleic acid (i.e., detecting a target nucleic acid existing in a cell or tissue), while as stated in Claim 1, determining the existence of the target nucleic acid in a PCR solution is a claimed feature and thus the amplified gene to be detected exists extracellularly. Thus, it has not been established that the references, considered alone or in combination teach or suggest the invention as claimed.

In order to support a prima facie case of obviouness, a combination of references mst teach each and every one of the claimed elements. Since the combination of Hu and Villeponteau et al. and Stapleton et al. does not teach each of the elements of Claims 5, 6-8 and 20, withdrawal of the rejection is respectfully requested.

Closing Remarks

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-1970, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-1970.

Respectfully submitted,

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